European Journal of Cancer 56 (2016) 122–130

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Clinical Trial

Retrospective inter- and intra-patient evaluation of trabectedin after best supportive care for patients with advanced translocation-related sarcoma after failure of standard chemotherapy

Nobuhito Araki [a,*], Shunji Takahashi [b], Hideshi Sugiura [c,d], Takafumi Ueda [e], Tsukasa Yonemoto [f], Mitsuru Takahashi [g], Hideo Morioka [h], Hiroaki Hiraga [i], Toru Hiruma [j], Toshiyuki Kunisada [k], Akihiko Matsumine [l], Akira Kawai [m]

[a] *Department of Orthopaedic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka 537-8511, Japan*
[b] *Department of Medical Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo 135-8550, Japan*
[c] *Department of Orthopaedic Surgery, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan*
[d] *Department of Physical Therapy, Nagoya University School of Health Sciences, Nagoya 461-8673, Japan*
[e] *Department of Orthopaedic Surgery, Osaka National Hospital, Osaka 540-0006, Japan*
[f] *Division of Orthopaedic Surgery, Chiba Cancer Center, Chiba 260-8717, Japan*
[g] *Division of Orthopaedic Surgery, Shizuoka Cancer Center Hospital, Shizuoka 411-8777, Japan*
[h] *Department of Orthopaedic Surgery, Keio University School of Medicine, Tokyo 160-8582, Japan*
[i] *Department of Orthopaedic Surgery, Hokkaido Cancer Center, Hokkaido 003-0804, Japan*
[j] *Department of Musculoskeletal Tumor Surgery, Kanagawa Cancer Center, Yokohama 241-8515, Japan*
[k] *Department of Medical Materials for Musculoskeletal Reconstruction, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama 700-8558, Japan*
[l] *Department of Orthopedic Surgery, Mie University Graduate School of Medicine, Mie 514-8507, Japan*
[m] *Department of Musculoskeletal Oncology, Rare Cancer Center, National Cancer Center Hospital, Tokyo 104-0045, Japan*

Received 4 June 2015; received in revised form 4 December 2015; accepted 14 December 2015
Available online 2 February 2016

KEY WORDS
Trabectedin;
Translocation-related

Abstract ***Aim:*** Our randomised phase II study showed the clinical benefit of trabectedin compared with best supportive care (BSC) in patients with advanced translocation-related sarcomas after the failure of standard chemotherapy. The aim of the present study was to evaluate efficacy and safety of trabectedin in the identical patients crossed over to trabectedin after

* *Corresponding author*: Department of Orthopaedic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi Higashinari-ku, Osaka 537-8511, Japan. Tel.: +81 6 6972 1181; fax: +81 6 6981 3000.
E-mail address: nobaraki@nifty.com (N. Araki).

http://dx.doi.org/10.1016/j.ejca.2015.12.014

sarcoma;
Soft tissue sarcoma;
Crossover;
Intra-patient;
Retrospective analysis

disease progression in the BSC arm of the randomised study.

Patients and methods: This was a single-arm study of the BSC patients of the randomised study in whom disease progressed. Trabectedin (1.2 mg/m^2) was administered over 24 h on day 1 of a 21-d treatment cycle. The efficacy and safety of trabectedin after BSC were evaluated and retrospectively compared with the results of the randomised study.

Results: Thirty patients crossed over to trabectedin. Median progression-free survival (PFS) was 7.3 months (95% confidence interval [CI]: 2.9–9.1) after crossover compared with 0.9 months (95% CI: 0.9–1.0) at BSC in the randomised study. PFS in the present study was comparable to that of the trabectedin arm in the randomised study. The number of patients with growth modulation index ≥1.33 was 25 (86%). Individual tumour volume was decreased in 11 patients after crossover. Adverse drug reactions (ADRs) were observed in 27 patients (96.4%). ADRs of grade III–IV were mainly bone marrow suppression and abnormal liver functions.

Conclusion: Trabectedin was revealed to be effective and well tolerated in the identical patients crossed over to trabectedin after disease progression in BSC.

The present study is registered with the Japan Pharmaceutical Information Center, number JapicCTI-121853.

1. Introduction

Soft tissue sarcomas (STS) are remarkably rare solid tumours, accounting for <1% of all adult malignancies, and classified into more than 50 histological subtypes. Molecular biology has recently played a strong role in STS diagnosis. One-third of STS subtypes are classified as translocation-related sarcomas (TRS) [1], which can be particularly interesting as a therapeutic target because TRS provide specific biological insights and mechanisms of action that may have an impact on prognosis or therapy [2]. Chemotherapy is used for the treatment of advanced STS. Over the past decades, doxorubicin, either alone or in combination with ifosfamide, has been used as first-line chemotherapy in most of STS subgroups; however, the response rates are as low as 20–30% [3,4]. Furthermore, therapeutic options after failure of doxorubicin and/or ifosfamide are limited [5].

Trabectedin is a marine-derived tetrahydroisoquinoline alkaloid [6]. Trabectedin is approved by the European Medicines Authority for the treatment of advanced STS in adults after failure of anthracyclines and ifosfamide or when unsuited to receive these agents based on the results of a pivotal phase II study, which indicated superior disease control by trabectedin given 1.5 mg/m^2 as a single infusion lasting 24 h every 3 weeks (q3week, 24 h) [7]. Trabectedin binds to the DNA minor groove, and has indirect anti-inflammatory and anti-angiogenic activity via tumour-associated macrophages [8]. It is noted that trabectedin also modulates the transcription of oncogenic fusion protein of TRS. Interestingly, the cytotoxic sensitivity of trabectedin correlates to the expression of different variants of the fusion protein [9,10].

We conducted a multicentre, open-label, randomised phase II study comparing trabectedin with the best supportive care (BSC) in patients with advanced TRS after failure of standard chemotherapy [11]. As previously reported, this randomised study showed the clinical benefit of trabectedin when administered at 1.2 mg/m^2 q3week, 24 h. The trabectedin dose of 1.2 mg/m^2 was based on the result of a phase I study in STS patients in Japan [12]. Seventy-six patients were randomised to receive either trabectedin or BSC in the randomised study, and 73 patients (37 in the trabectedin arm and 36 in the BSC arm) were included in the efficacy analysis [11].

The aim of the present study was to evaluate the efficacy and safety of trabectedin in patients crossed over to trabectedin after disease progression while undergoing BSC. We report a retrospective comparison of these two studies.

2. Patients and methods

2.1. Patients

Patients who were assigned to BSC in the randomised study and whose disease progressed afterwards according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 were allowed to crossover to trabectedin (Fig. 1). During BSC, patients did not receive anti-tumour therapy but did receive treatment to relieve symptoms induced by primary disease and improve quality of life. Most eligibility criteria of the present study were the same as in the randomised study [11]. In brief, eligible patients were pathologically diagnosed as a subtype of TRS: myxoid/round cell liposarcoma (MRCL), synovial sarcoma (SS), alveolar

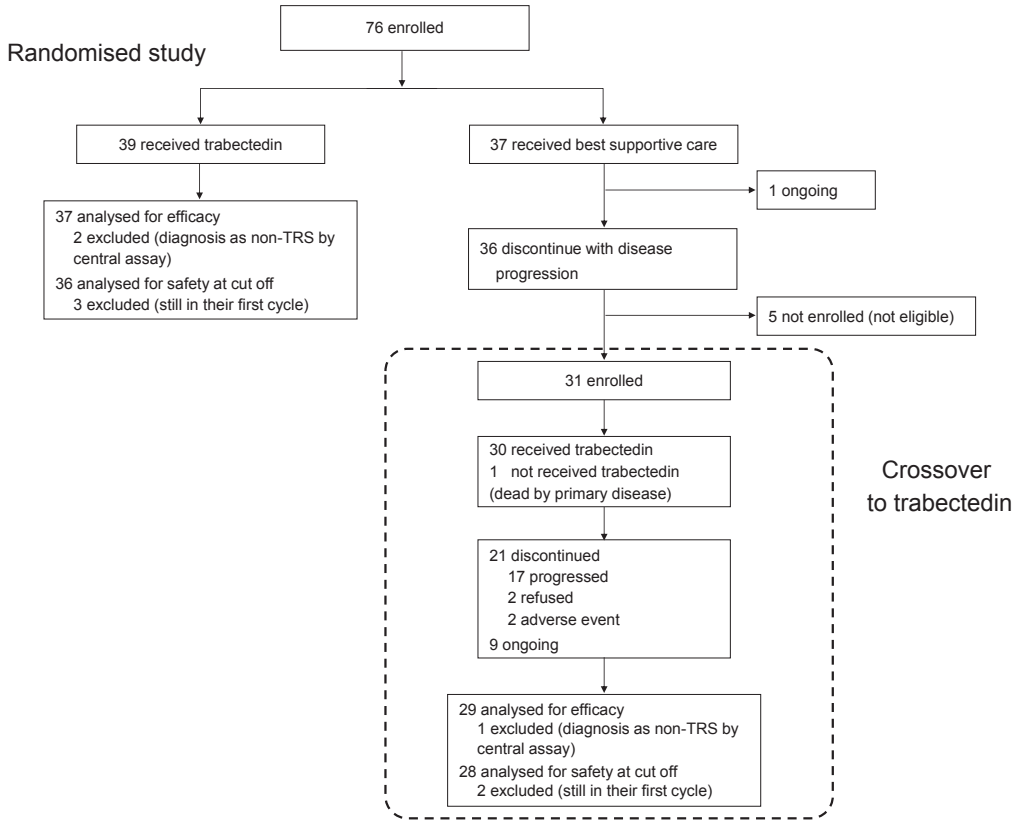

Fig. 1. Patient disposition. TRS: translocation-related sarcomas.

rhabdomyosarcoma, extraskeletal Ewing sarcoma/primitive neuroectodermal tumour, dermatofibrosarcoma protuberans, low grade fibromyxoid sarcoma, alveolar soft part sarcoma, clear cell sarcoma, angiomatoid fibrous histiocytoma, desmoplastic small round cell tumour, extraskeletal myxoid chondrosarcoma, mesenchymal chondrosarcoma, giant cell fibroblastoma, or endometrial stromal sarcoma.

The study protocol and the informed consent documents were approved by the institutional review board at each study site. All patients gave written informed consent before the initiation of any study-specific procedures. The study was conducted in accordance with the ethical principles originating in or derived from the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and locally applicable laws and regulations. Trabectedin was supplied by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).

2.2. Treatment and assessments

Trabectedin (standard starting dose; 1.2 mg/m^2) was given via a central venous line over 24 h from 30 min after administration of dexamethasone and a 5-HT_3 receptor antagonist as antiemetic pretreatment on day 1 of a 21-d cycle. The study treatment was repeated until disease progression, unmanageable toxicity, patient refusal, or delay for >21 d (one cycle) occurred due to toxicity. Tumour assessment by computed tomography or magnetic resonance imaging was repeated weeks 6, 12, 18, 24, and every 8 weeks thereafter in the present study, while that of the randomised study was repeated weeks 4, 8, 12, 18, 24, and every 8 weeks thereafter.

Efficacy end-points were objective response rate [ORR: the proportion of patients who achieved complete response (CR) or partial response (PR)], disease control rate (DCR: the proportion of patients with CR, PR, or stable disease), progression-free survival (PFS: the time from the day of enrollment in each study until radiologic progression assessed by central radiology imaging review or death by any cause), progression-free rate (PFR) at 3 and 6 months (Kaplan–Meier estimate at each interval), and overall survival (OS: the time from the day of enrollment in each study until death by any cause). Time to progression (TTP) was defined as the time from the day of enrollment in each study until radiologic progression assessed by central radiology imaging review. Objective response was assessed according to RECIST version 1.1. Adverse events (AEs) were graded according to Common Terminology Criteria of Adverse Events version 4.03.

Table 1
Demographics and baseline characteristics of patients.

	Trabectedin arm in randomised study ($N = 37$)[a]		BSC arm in randomised study ($N = 29$)		Crossed over to trabectedin ($N = 29$)	
	n	(%)	*n*	(%)	*n*	(%)
Gender						
Male	21	(57)			17 (59)	
Female	16	(43)			12 (41)	
Age (years)						
Median [range]	39.0 [21–77]				38.0 [25–60]	
Eastern Cooperative Oncology Group performance status						
0	22	(60)	20	(69)	16	(55)
1	15	(41)	9	(31)	13	(45)
Histological type[b]						
Myxoid liposarcoma/round cell liposarcoma	14	(38)			8 (28)	
Synovial sarcoma	7	(19)			10 (35)	
Mesenchymal chondrosarcoma	3	(8)			3 (10)	
Extraskeletal Ewing sarcoma/primitive neuroectodermal tumour	3	(8)			2 (7)	
Alveolar soft part sarcoma	3	(8)			1 (3)	
Alveolar rhabdomyosarcoma	2	(5)			3 (10)	
Extraskeletal myxoid chondrosarcoma	2	(5)			0 (0)	
Dermatofibrosarcoma protuberans	1	(3)			0 (0)	
Angiomatoid fibrous histiocytoma	1	(3)			0 (0)	
Clear cell sarcoma	1	(3)			1 (3)	
Desmoplastic small round cell tumour	0	(0)			1 (3)	
Histological grade[c]						
Low	2	(5)			0 (0)	
Median	8	(22)			8 (28)	
High	23	(62)			18 (62)	
Not assessed or unknown	4	(11)			3 (10)	
Translocation						
Positive	31	(84)			25 (86)	
Primary lesion						
Lower limbs	21	(57)			15 (52)	
Abdomen/pelvises	3	(8)			4 (14)	
Intrathoracic	3	(8)			0 (0)	
Neck	2	(5)			1 (3)	
Face	1	(3)			4 (14)	
Retroperitoneum	1	(3)			2 (7)	
Other	6	(16)			3 (10)	
Site by central radiology imaging review[d]						
Lung	25	(68)	17	(59)	18	(62)
Peritonea	12	(32)	9	(31)	10	(35)
Lymph node	11	(30)	7	(24)	9	(31)
Pleura	11	(30)	7	(24)	8	(28)
Bone	11	(30)	4	(14)	5	(17)
Muscle	9	(24)	6	(21)	7	(24)
Other	10	(27)	4	(14)	5	(17)
Sum of the diameters of target lesions (mm)						
Median [range]	91.70 [10.0–443.9]		93.30 [16.5–305.0]		134.20 [25.7–422.7]	
Time from initial diagnosis to enrolled date (months)						
Median [range]	31.50 [3.4–225.0]		35.00 [2.5–166.7]		36.60 [2.7–167.3]	
Number of regimen of prior systemic anticancer agents						
Median [range]	1.0 [0–3]				2.0 [0–4]	
Post-treatment[e]						
Yes	18	(49)	29	(100)	16	(55)

BSC, best supportive care.
Analysis set: Full analysis set (FAS).
[a] Data reported by Kawai et al. [11].
[b] Diagnosed at central pathological assay.
[c] Assessed according to French Fédération Nationale des Centres de Lutte Contre Le Cancer system system.
[d] Multiple answers were allowed.
[e] All patients in BSC arm in the randomised study were crossed over to trabectedin because six patients who were not crossed over were excluded.

2.3. Statistical analysis

The efficacy was analysed in the full analysis set, which was defined as patients who were histologically diagnosed as TRS by central pathological assay, received trabectedin at least once, and had any tumour assessment or survival follow-up. The Kaplan–Meier method was used to estimate PFS and OS, including 95% confidence interval (CI). The inter-patient variability of PFS and OS in the trabectedin arm of the randomised study and crossover study were retrospectively evaluated. The growth modulation index (GMI), which is used as a measure of the activity of second-line treatment, is calculated as follows; $GMI = TTP_{present\ study}/TTP_{BSC}$ [13,14]. GMI $\geq$1.33 has been suggested as a criteria of active drug. Intra-patient variability of change from baseline in tumour volume was retrospectively compared between the BSC arm of the randomised study and that of trabectedin in the crossover study, and was illustrated by individual patients. The safety was analysed in the all-treated population, defined as the patients who received trabectedin at least once.

The data cut-off date of both studies was February 8, 2014.

3. Results

Of the 36 patients whose disease progressed following initial assignment to BSC in the randomised study, five patients in the BSC arm were not enrolled in this study; two patients received radiotherapy as a post-treatment, two did not have any post-treatment, and one died because of disease progression 1 d after termination of the randomised study. Remaining 31 patients were enrolled in the present study between August 20, 2012 and January 30, 2014. Of the 31 patients enrolled, 30 patients crossed over to trabectedin because one patient died before receiving trabectedin (Fig. 1), and a total of six patients (16%) of the BSC arm were not able to crossover to trabectedin. Of the 30 patients crossed over to trabectedin, the efficacy of trabectedin in 29 patients was retrospectively compared in the trabectedin and BSC arms, after excluding one patient who was diagnosed as non-TRS by central assay.

The patient characteristics are listed in Table 1. Major subtypes of TRS were SS and MRCL. The median sum of diameters of target lesions by central radiology image review in the present study was 134.2 mm (range, 25.7–422.7). The median total number of

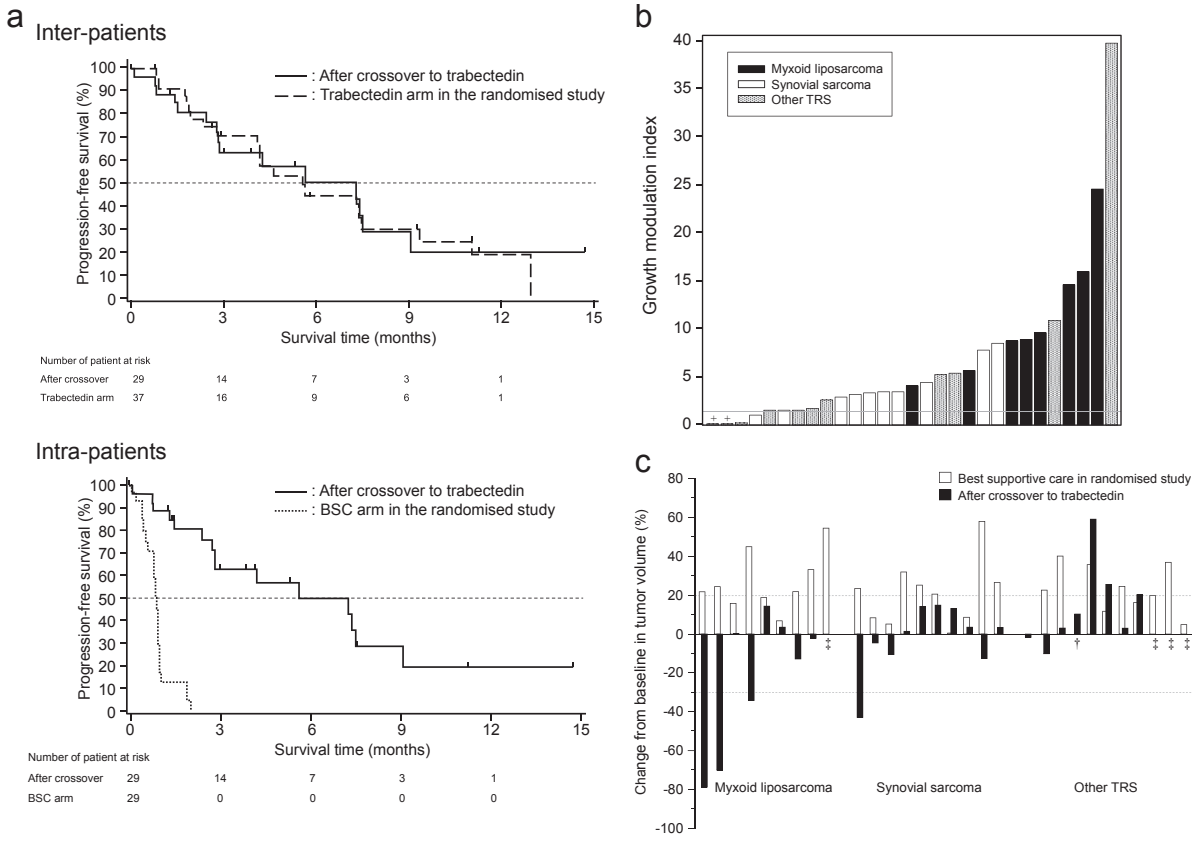

Fig. 2. (a) Comparison of Kaplan–Meier curve of inter- and intra-patient progression-free survival (PFS), (b) growth modulation index, (c) individual intra-patient change from baseline in tumor volume. +Censored observation at cut off; †patients with non-evaluable target lesion in the randomised study; ‡patients with non-evaluable target lesion after crossover to trabectedin. Other TRS: Subtypes other than myxoid liposarcoma and synovial sarcoma. TRS, translocation-related sarcomas; BSC, best supportive care.

trabectedin cycles was 4.0 (range, 1–14). The dose was reduced in three patients (10.3%).

Median PFS was 7.3 months (95% CI: 2.9–9.1) in the present study, while in the randomised study median PFS for trabectedin and BSC was 5.6 months (95% CI: 4.1–7.5) and 0.9 months (95% CI: 0.9–1.0). Comparisons of Kaplan–Meier curves of inter- and intra-patient PFS are shown in Fig. 2a. Twenty five patients (86%) had GMI ≥1.33 (Fig. 2b). Fig. 2c shows change from baseline in tumour volume by individual patients. The PFR at 3 and 6 months was 63.0% (95% CI: 43.5–82.4) and 50.1% (95% CI: 27.7–72.4), while in the randomised study PFR was 70.3% (95% CI: 53.9–86.8) and 44.0% (95% CI: 24.4–63.6), respectively. ORR and DCR are 14% and 69% in all subtypes, 38% and 100% in MRCL as listed in Table 2. TRS subtypes with PR to trabectedin were MRCL in three patients and SS in one patient. Radiological images of two of the PR cases after crossover to trabectedin are shown in Fig. S1.

Median OS was 10.3 months (95% CI: 6.6–not reached) in the present study (Fig. 3). The number of deaths was 11 (37.9%), and cause of death in all cases was disease progression. The number of censored cases was 18 (62.1%), because these patients were alive at the cut-off date.

Safety was assessed in 28 patients at data cutoff. Sixteen serious adverse events were observed in nine patients, and serious adverse drug reactions (SADRs) were 12 in six patients. Among the 12 SADRs, four events of bone-marrow suppression occurred in three patients. These SADRs were recovered by adequate treatment. AEs occurred in all patients, and 96.4% of patients had drug-related AEs (Table 3). Highly frequent AEs of grade III or IV were mainly bone marrow suppression and abnormal liver functions. Two patients withdrew from the study due to toxicity (nausea, decreased appetite, vomiting, malaise, aspartate aminotransferase increased, and alanine aminotransferase increased). No drug-related deaths were found during the study.

4. Discussion

In the present study, we found that trabectedin was effective and tolerable in patients with advanced TRS after failure of standard chemotherapy even if patients had passed through the duration of BSC.

We used only the data of patients in the BSC arm who crossed over to trabectedin to compare the efficacy in identical patients. Exclusion of six patients who did not crossover to trabectedin from the retrospective analysis population would cause a potential bias, predicting better outcome, because five of six patients died within 5 months from the enrollment in the randomised study, shorter than the overall median OS.

Patient characteristics in the present study were similar to those in the randomised study, because the present study was a continuation of the randomised study, and patient characteristics were well balanced in the randomised study. However, in intra-patient comparison, median size of the target lesion in the present

Table 2
Tumour response by RECIST ver.1.1; overall and per histological subtype.

	Trabectedin arm of randomised study		Crossover to trabectedin	
	n	(%)	*n*	(%)
All subtypes	(N = 37)[a]		(N = 29)	
CR	0	(0)	0	(0)
PR	3	(8)	4	(14)
SD	21	(57)	16	(55)
PD	7	(19)	4	(14)
NE	6	(16)	5	(17)
Response rate (CR+PR)	3	(8)	4	(14)
95% CI (%)	[1.7–21.9]		[3.9–31.7]	
Disease control rate (CR+PR+SD)	24	(65)	20	(69)
95% CI (%)	[47.5–79.8]		[49.2–84.7]	
Myxoid/round-cell liposarcoma	(n = 14)		(n = 8)	
CR	0	(0)	0	(0)
PR	3	(21)	3	(38)
SD	8	(57)	5	(63)
PD	1	(7)	0	(0)
NE	2	(14)	0	(0)
Response rate (CR+PR)	3	(21)	3	(38)
95% CI (%)	[4.7–50.8]		[8.5–75.5]	
Disease control rate (CR+PR+SD)	11	(79)	8	(100)
95% CI (%)	[49.2–95.3]		[63.1–100.0]	
Synovial sarcoma	(n = 7)		(n = 10)	
CR	0	(0)	0	(0)
PR	0	(0)	1	(10)
SD	4	(57)	8	(80)
PD	2	(29)	0	(0)
NE	1	(14)	1	(10)
Response rate (CR+PR)	0	(0)	1	(10)
95% CI (%)	[0.0–41.0]		[0.3–44.5]	
Disease control rate (CR+PR+SD)	4	(57)	9	(90)
95% CI (%)	[18.4–90.1]		[55.5–99.7]	
Other TRS	(n = 16)		(n = 11)	
CR	0	(0)	0	(0)
PR	0	(0)	0	(0)
SD	9	(56)	3	(27)
PD	4	(25)	4	(36)
NE	3	(19)	4	(36)
Response rate (CR+PR)	0	(0)	0	(0)
95% CI (%)	[0.0–20.6]		[0.0–28.5]	
Disease control rate (CR+PR+SD)	9	(56)	3	(27)
95% CI (%)	[29.9–80.2]		[6.0–61.0]	

Other TRS, subtypes other than myxoid liposarcoma and synovial sarcoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; RECIST, Response Evaluation Criteria in Solid Tumours; TRS, translocation-related sarcomas; CI, confidence interval.

[a] Data reported by Kawai et al. [11].

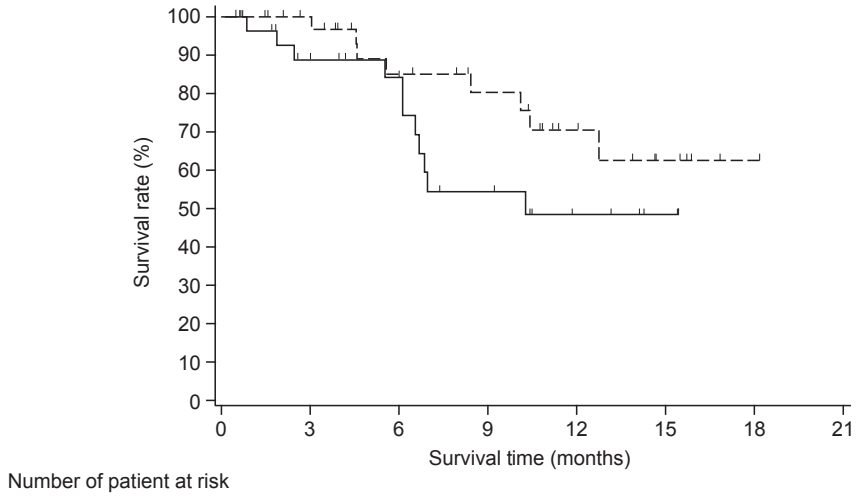

Fig. 3. Kaplan–Meier plot of overall survival. Overall survival of patients crossed over to trabectedin after randomised to BSC (—) and those initially randomised to the trabectedin arm (---). BSC, best supportive care.

study was approximately 40 mm larger and the number of patients with performance status 1 was higher than that in the BSC arm. In inter-patient comparison, median size of target lesion, time from initial diagnosis to enrolled date, and number of regimens were slightly different. These could have been affected by primary disease progression during BSC. Numbers of dose reduction or discontinuation, dose intensity, and relative dose intensity were similar to those of the trabectedin arm in the randomised study.

Median PFS in the BSC arm of the randomised study was dramatically improved by crossing over to trabectedin. Although patient characteristics in the present study tended to be worse than those in the trabectedin arm in the randomised study, PFS in the present study was comparable to that of the trabectedin arm in the randomised study.

Most of the patients progressed within 1 month in BSC. Although disease is thought to progress as time passes, 86% of patients had GMI $\geq$1.33, which means $\geq$33% improvement by trabectedin. Individual tumour volume decreased in 11 patients after crossover. In the patients whose tumour volume was not decreased after crossover, progression was suppressed. These findings indicate that the disease progression was controlled well by trabectedin.

Le Cesne et al. [15] reported that median PFS in TRS was 4.1 months (95% CI, 2.8–6.1) in a retrospective analysis. The present study showed similar PFS in patients with TRS subtypes crossed over to 1.2 mg/m^2 trabectedin.

This crossover study design with intra-patient retrospective analysis would be a useful method for confirming the efficacy and safety of a study drug in a limited number of clinical studies, as previously reported by Zalcberg et al. [16] in a study of imatinib in gastrointestinal stromal tumour.

PFR of 63.0% at 3 months and 50.1% at 6 months after crossover to trabectedin, as the median of third-line treatment, notably exceeded the cutoff criteria for second-line treatment of advanced STS, established by the European Organisation for Research and Treatment of Cancer (39% at 3 months and 14% at 6 months) [17]. ORR and DCR after crossover were nearly equal to those in the trabectedin arm in the randomised study. It is noteworthy that DCR was 100% in MRCL patients after crossover. Median OS after crossover was 10.3 months at the cut-off date. The observation period was short at about 18 months, and therefore the contribution of trabectedin to OS needs promising further investigation.

As recently Le Cesne et al. [18] have reported that continuation of trabectedin affects PFS prolongation in STS patients, trabectedin has become a more important role on the treatment for STS.

Major drug-related AEs with a high degree of severity were myelosuppression and abnormal liver functions. These were mostly reversible and manageable by adequate treatment or arrangement of treatment interval, with no cumulative toxicity with repeating cycles. The safety profiles of trabectedin in the present study were similar to those in the trabectedin arm in the randomised study [11] and other studies of 1.5 mg/m^2 of trabectedin [19].

In conclusion, to our knowledge, this is the first intra-patient comparison of trabectedin with BSC. Trabectedin was effective and tolerable even in patients crossed over to trabectedin after disease progression within 1

Table 3
Trabectedin-related adverse events that occurred in ≥10% of patients.

	Trabectedin arm in randomised study ($N = 36$)[a]		Crossed over to trabectedin ($N = 28$)	
	≥G1	≥G3	≥G1	≥G3
	n (%)	*n* (%)	*n* (%)	*n* (%)
Any adverse events	36 (100)	34 (94)	28 (100)	26 (93)
Any adverse drug reactions	36 (100)	33 (92)	27 (96)	26 (93)
Adverse drug reactions (≥10% of patients)				
Clinical findings				
Nausea	32 (89)	3 (8)	25 (89)	1 (4)
Decreased appetite	21 (58)	2 (6)	20 (71)	3 (11)
Constipation	17 (47)	0 (0)	12 (43)	0 (0)
Malaise	16 (44)	0 (0)	18 (64)	0 (0)
Vomiting	14 (39)	0 (0)	9 (32)	0 (0)
Anaemia	11 (31)	7 (19)	7 (25)	7 (25)
Fatigue	6 (17)	1 (3)	5 (18)	0 (0)
Diarrhoea	6 (17)	1 (3)	3 (11)	0 (0)
Stomatitis	6 (17)	0 (0)	3 (11)	0 (0)
Pyrexia	6 (17)	0 (0)	3 (11)	0 (0)
Dysgeusia	5 (14)	0 (0)	3 (11)	0 (0)
Myalgia	5 (14)	0 (0)	3 (11)	0 (0)
Febrile neutropenia	5 (14)	5 (14)	5 (18)	5 (18)
Oedema peripheral	4 (11)	0 (0)	2 (7)	0 (0)
Hiccups	2 (6)	0 (0)	3 (11)	0 (0)
Non-haematological laboratory value				
Alanine aminotransferase increased	24 (67)	22 (61)	19 (68)	19 (68)
Aspartate aminotransferase increased	17 (47)	15 (42)	18 (64)	15 (54)
Gamma-glutamyltransferase increased	10 (28)	9 (25)	12 (43)	12 (43)
Blood bilirubin increased	4 (11)	0 (0)	2 (7)	0 (0)
Blood creatine phosphokinase increased	4 (11)	1 (3)	1 (4)	0 (0)
Blood alkaline phosphatase increased	3 (8)	2 (6)	6 (21)	0 (0)
Haematological laboratory value				
Neutrophil count decreased	30 (83)	24 (67)	26 (93)	24 (86)
White blood cell count decreased	20 (56)	20 (56)	19 (68)	19 (68)
Platelet count decreased	13 (36)	6 (17)	11 (39)	6 (21)
Lymphocyte count decreased	8 (22)	8 (22)	6 (21)	6 (21)

BSC, best supportive care
Analysis set: all trabectedin-treated patients.
Total of five patients (two patients crossed over to trabectedin and three patients in the randomised study in the BSC arm in the randomised study) were excluded from this analysis because they were still in their first treatment cycle at the analysis cutoff date.
Grade was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[a] Data reported by Kawai et al. [11].

month in BSC. The results of the present study make the effectiveness and safety of trabectedin confirmed in the randomised study more robust. Our findings confirm the role of trabectedin for patients with TRS after failure of standard chemotherapy.

Conflict of interest statement

NA reports grants and non-financial support from Taiho Pharmaceutical, GSK, Eisai, Japan Clinical Oncology Group, and MSD.

ST reports grants and personal fees from Taiho Pharmaceutical, Eisai, Boehringer Ingelheim, Novartis Pharma, Bayer, Daiichi-Sankyo Company, Merck, and Astellas Pharma; grants from GSK, Chugai Pharmaceutical, Zenyaku Kogyo, Sanofi, Otsuka Pharmaceutical, Pfizer, and Japan Clinical Oncology Group; grants, personal fees, and non-financial support from AstraZeneca.

HS reports grants, personal fees, and non-financial support from Taiho Pharmaceutical; grants and non-financial support from GSK, Eisai, and MSD.

TU reports grants and non-financial support from Taiho Pharmaceutical, Eisai and MSD; grants, personal fees, and non-financial support from Daiichi-Sankyo Company and GSK.

TY reports grants, personal fees, and non-financial support from Taiho Pharmaceutical; personal fees from Daiichi-Sankyo Company; grants and non-financial support from GSK and Merck.

MT reports grants, personal fees, and non-financial support from Taiho Pharmaceutical.

HM reports grants, personal fees, and non-financial support from Taiho Pharmaceutical, Daiichi-Sankyo Company and GSK; grants and non-financial support from Eisai; and personal fees from Novartis Pharma.

HH reports grants and non-financial support from Taiho Pharmaceutical, GSK, Eisai, and MSD; grants from Ono Pharmaceutical, Daiichi-Sankyo Company, Ministry of Health, Labour and Welfare, Center for Clinical Trials, Japan Medical Association, and National Cancer Center.

TH reports grants, personal fees, and non-financial support from Taiho Pharmaceutical; personal fees from GSK.

TK reports grants and non-financial support from Taiho Pharmaceutical; non-financial support from Japan Clinical Oncology Group.

AM reports grants and non-financial support from Taiho Pharmaceutical, GSK, Eisai, MSD, and Japan Clinical Oncology Group.

AK reports grants, personal fees, and non-financial support from Taiho Pharmaceutical, GSK, Eisai, and MSD; grants and non-financial support from Japan Clinical Oncology Group.

Role of the funding source

This study was funded by Taiho Pharmaceutical Co., Ltd. Editorial and writing assistance was provided by SunFlare Co., Ltd., funded by Taiho Pharmaceutical

Co., Ltd. The costs of publication of this article were defrayed in part by the payment of page charges.

Acknowledgement

All authors were involved in the study design and interpretation of the data. The National Institute of Biomedical Innovation (Osaka, Japan) promoted Taiho Pharmaceutical Co., Ltd. in development of trabectedin under orphan designation in Japan. Pharma Mar, SA. (Madrid, Spain) kindly reviewed this manuscript. The authors thank all participating patients and their families, the study investigators, study nurses, study monitors, data manager, and all other members of this study team. They also thank Noriyuki Masuda (Kitasato University School of Medicine, Kanagawa) for participating in this study as a medical advisor, Hirokazu Watanabe (National Cancer Center Hospital, Tokyo) for participating in this study as the medical advisor for tumour assessment by RECIST, members of the data monitoring and safety committee (Dr. Junji Furuse, Kyorin University School of Medicine, Tokyo; Dr. Yoshiyuki Ueno, Yamagata University, Yamagata; Dr. Hitoshi Arioka, Yokohama Rosai Hospital, Yokohama; Dr. Makoto Nishio, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo), and central radiology imaging review committee (LISIT Co., Ltd. and Musashi Image Joho Co., Ltd.). The authors thank Dr. Tetsuji Asao (SunFlare Co., Ltd., Tokyo, Japan) for medical writing services, which were funded by Taiho Pharmaceutical Co., Ltd.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2015.12.014.

References

[1] Mertens F, Antonescu CR, Hohenberger P, Ladanyi M, Modena P, D'Incalci M, et al. Translocation-related sarcomas. Semin Oncol 2009;36(4):312–23.
[2] Borden EC, Baker LH, Bell RS, Bramwell V, Demetri GD, Eisenberg BL, et al. Soft tissue sarcomas of adults: state of the translational science. Clin Cancer Res 2003;9(6):1941–56.
[3] Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, et al. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol 1993;11(7):1269–75.
[4] Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995;13(7):1537–45.
[5] Sharma S, Takyar S, Manson SC, Powell S, Penel N. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review. BMC Cancer 2013;13:385.
[6] Erba E, Bergamaschi D, Bassano L, Damia G, Ronzoni S, Faircloth GT, et al. Ecteinascidin-743 (ET-743), a natural marine compound, with a unique mechanism of action. Eur J Cancer 2001;37(1):97–105.
[7] Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27(25):4188–96.
[8] D'Incalci M, Galmarini CM. A review of trabectedin (ET-743): a unique mechanism of action. Mol Cancer Ther 2010;9(8):2157–63.
[9] Grohar PJ, Griffin LB, Yeung C, Chen QR, Pommier Y, Khanna C, et al. Ecteinascidin 743 interferes with the activity of EWS-FLI1 in Ewing sarcoma cells. Neoplasia 2011;13(2):145–53.
[10] Di Giandomenico S, Frapolli R, Bello E, Uboldi S, Licandro SA, Marchini S, et al. Mode of action of trabectedin in myxoid liposarcomas. Oncogene 2014;33(44):5201–10.
[11] Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomized, open-label, phase 2 study. Lancet Oncol 2015;16(4):406–16.
[12] Ueda T, Kakunaga S, Ando M, Yonemori K, Sugiura H, Yamada K, et al. Phase I and pharmacokinetic study of trabectedin, a DNA minor groove binder, administered as a 24-h continuous infusion in Japanese patients with soft tissue sarcoma. Invest New Drugs 2014;32(4):691–9.
[13] Von Hoff DD. There are no bad anticancer agents, only bad clinical trial designs–twenty-first Richard and Hinda Rosenthal Foundation Award Lecture. Clin Cancer Res 1998;4(5):1079–86.
[14] Penel N, Demetri GD, Blay JY, Cousin S, Maki RG, Chawla SP, et al. Growth modulation index as metric of clinical benefit assessment among advanced soft tissue sarcoma patients receiving trabectedin as a salvage therapy. Ann Oncol 2013;24(2):537–42.
[15] Le Cesne A, Cresta S, Maki RG, Blay JY, Verweij J, Poveda A, et al. A retrospective analysis of antitumour activity with trabectedin in translocation-related sarcomas. Eur J Cancer 2012;48(16):3036–44.
[16] Zalcberg JR, Verweij J, Casali PG, Le Cesne A, Reichardt P, Blay JY, et al. Outcome of patients with advanced gastrointestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005;41(12):1751–7.
[17] Van Glabbeke M, Verweij J, Judson I, Nielsen OS, EORTC Soft Tissue and Bone Sarcoma Group. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 2002;38(4):543–9.
[18] Le Cesne A, Blay JY, Domont J, Tresch-Bruneel E, Chevreau C, Bertucci F, et al. Interruption versus continuation of trabectedin in patients with soft-tissue sarcoma (T-DIS): a randomised phase 2 trial. Lancet Oncol 2015;16(3):312–9.
[19] Martin-Liberal J, Judson I. Safety evaluation of trabectedin in treatment of soft-tissue sarcomas. Expert Opin Drug Saf 2013;12(6):905–11.